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Mini-Review

Intersexuality and Gender Identity Differentiation

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Introduction

Over the past couple of decades, there have been some remarkable advances in understanding the biological processes that underlie both normal and abnormal physical sex differentiation.[1–2] During this same time period, there has also been progress in understanding the mechanisms—both biological and psychological—that underlie psychosexual differentiation (a term that I define and decompose below) in people whose physical sex differentiation is normal and in people where it is not.[3–4]

Alongside the advances in these two domains (perhaps because of them or perhaps in spite of them—that will be up to the reader to judge), there has been a third development, namely that the clinical management of disorders of physical sex differentiation—intersexuality—is in a state of great flux, debate, and controversy. One might even go so far as to say that the field is in crisis. There are, for example, various concerns and objections about the use of surgical interventions to "normalize" the ambiguous genitalia of people with physical intersex conditions, particularly in infancy or childhood and prior to the time that the patient can provide informed consent.[5–7] Some critics have charged that genital surgery is merely cosmetic, perhaps akin to a face-lift, and is not medically necessary, and that it is performed primarily to appease anxious parents. Moreover, these critics claim that surgical correction to the genitalia (e.g., feminizing genitoplasty) in infancy or early childhood impairs sexual function in adulthood. Holmes[8] provides a good example of this critique. Holmes was born with an enlarged clitoris and eventually received the diagnosis of progestin-induced hermaphroditism. For reasons that are not entirely clear, Holmes had multiple medical evaluations and it was only at the age of 7 that she received genital surgery, which involved a complete clitoridectomy. As Holmes puts it, had she not received this surgery, "I could have functioned as a bisexual-homosexual-heterosexual . . . all in the same activity . . . All the things I might have grown up to do, all the possibilities went down the hall with my clitoris to the pathology department. Me and my remains went to the recovery room and have not yet emerged" (pp. 50–52).

Other critics have called for a moratorium on surgical interventions until the status of previously treated patients are followed up with greater precision.[9] Although guidelines for psychological counseling have been available for some time,[10–11] there has been a resurgence of discussion about the uneven quality of psychological counseling that is available to people with physical intersex conditions and their families.[12] Other aspects of the current debate have been fueled by critics of the "medical model," who utilize a "social constructionist" approach in appraising the extant literature.[13–15] Why, such critics ask, is it so important to decide whether an infant should be raised as a boy or as a girl; and some even suggest that physicians and other health professionals consider alternative options, such as raising intersex infants in a "third" gender or even no gender at all.

In this article, I will begin by providing a brief overview of relevant terminology. I will then review one specific aspect of the contemporary literature on intersexuality, namely what is known about gender identity formation and differentiation. I have chosen this specific topic for a couple of reasons. First, there has been, over

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the years, periodic debate regarding the question of the "appropriate" sex assignment and subsequent gender of rearing of infants and children with physical intersex conditions, primarily in relation to the formulation originally introduced and then later amplified by the work of Money and his colleagues at Johns Hopkins Hospital in Baltimore beginning in the 1950s. Second, over the last few years, this debate has resurfaced, with even greater force and intensity, following the publication of the David Reimer case.[16–17] It is timely, therefore, to review the empirical database on gender identity formation in people with physical intersex conditions and then to draw some provisional conclusions about the candidate explanations that best account for the pattern of results.

Parameters of Biological Sex

Over time in the medical literature, intersexuality has become the preferred umbrella term used to encompass the diverse class of syndromes characterized by some abnormality or anomaly in physical sex differentiation. Thus, the term intersexuality can be understood to represent a broader class of syndromes than those that have been traditionally subsumed under terms like true hermaphroditism, female pseudohermaphroditism, and male pseudohermaphroditism, which were used by Klebs 125 years ago, in one of the first taxonomic efforts to classify physical intersex conditions.[18]

Efforts to devise accurate taxonomic systems are, of course, dependent on our knowledge of the multiple parameters that constitute biological sex (Table 1). Thus, for example, in Klebs' time, sex chromosome abnormalities were not part of any system of classification—after all, it was only in the 1950s that reliable techniques were developed to karyotype the sex chromosomes.[19] Klebs' proposed system of classification placed great emphasis on the importance of certain diagnostic techniques, including clinical microscopy, laparotomy, and biopsy. The insistence on histologic analysis appeared to have resulted in the nature of the gonads becoming the final arbiter in deciding upon the "true sex" of the hermaphrodite, a development that had substantial implications. As noted by Meyer-Bahlburg,[20] among others, the notion of a "true sex" in intersexuality is problematic. Given that a person's physical sex is multidimensional in nature, there is no reason to insist that one parameter should necessarily hold precedence over another. Thus, from a descriptive point of view all that is required is an accurate delineation of the physical sex parameters that are affected in particular intersex syndromes.

Parameters of Psychosexual Differentiation

Many clinicians and researchers deconstruct the umbrella term, psychosexual differentiation, into four component parts. It is important, therefore, to define these terms and to keep them in mind when thinking about the clinical issues under consideration.

Table 1. Parameters of Biological Sex

1. Chromosomal Sex
2. Gonadal Sex[a]
3. Hormonal Sex
4. Internal Reproductive Structures
5. External Genitalia
6. "Brain" Sex[b]

From Migeon and Wisniewski.[21]

[a]Although it has long been surmised that the presence of the Y chromosome was necessary for the gonads to differentiate along male lines (i.e., testicular differentiation), it was only in 1990 that the "testis-determining factor" (TDF) was identified.[2] As described by Haqq and Donahoe,[22] the TDF is located on the short arm of the Y chromosome, with subsequent identification of SRY (the sex-determining gene region of the Y chromosome). In addition, Mullerian inhibiting substance is another protein involved in the temporal sequence of events that leads to male sex differentiation, as it results in the regression of the Mullerian duct, the anlagen of the uterus, the fallopian tubes, and the upper vagina. It is well known, however, that even in the presence of a normal SRY and normal production of testosterone from the fetal gonad, the fetus must also have operative androgen receptors; otherwise, the external genitalia will differentiate along female lines although the vaginal canal lacks depth and there are no internal female organs.

[b]Over the past couple of decades, there has, of course, been great interest in the possibility that the human brain has certain sex-dimorphic characteristics.[4] The existence of such putative anatomic and functional properties has not, however, been part of any formal taxonomic system of physical intersex conditions. Ironically, however, the assumption that there is some kind of CNS sex dimorphism has played a great role in the current debate about gender identity differentiation among people with physical intersex conditions.

Gender Identity

As a term, *gender identity* was introduced into the professional lexicon by Hooker, a psychologist, and Stoller, a psychoanalyst, almost simultaneously in the early 1960s.[23–24] It refers to a young child's developing a fundamental sense of belonging to one sex and not the other. Measurement of gender identity can be assessed with structured verbal interview techniques.[25]

Gender Role

The term *gender role* has been used extensively by developmental psychologists to refer to behaviors, attitudes, and personality traits that a society, in a given culture and historical period, designates as masculine or feminine, that is, more "appropriate" to or typical of the male or female social role. In children, the measurement of gender role behavior includes several easily observable phenomena, including affiliative preference for same-sex vs. opposite-sex peers, fantasy roles, toy inter-

ests, dress-up play, and interest in rough-and-tumble play.[3]

Sexual Orientation

The term *sexual orientation* is defined by a person's relative responsiveness to sexual stimuli. The most salient dimension of sexual orientation is probably the sex of the person to whom one is attracted sexually. This stimulus class is obviously how one defines a person's sexual orientation as heterosexual, bisexual, or homosexual. In contemporary sexological research, sexual orientation is often assessed by psychophysiological techniques, such as penile plethysmography or vaginal photoplethysmography,[26–27] although structured interview assessments have become increasingly common, particularly when respondents do not have a compelling reason to conceal their sexual orientation.

Sexual Identity

It is important to uncouple the construct of sexual orientation from the construct of *sexual identity*. A person may, for example, be predominantly aroused by homosexual stimuli, yet not regard himself or herself as "a homosexual," for whatever reason. Sociologists, particularly those of the "social scripting" and "social constructionist" schools, have articulated this notion most forcefully, arguing that the incorporation of sexual orientation into one's sense of identity is a relatively recent phenomenon, culturally variable, and the result of a complex interplay of sociohistorical events. Anthropologists, such as Herdt, who have described ritualized, age-structured homosexual behavior in non-Western cultures, note that such behavior is not at all tied to a homosexual sexual identity, but rather is a rite of passage to mature, adult heterosexuality.[28]

In contemporary Western culture, there are many individuals who are primarily or exclusively sexually responsive to same-sex persons yet do not adopt a homosexual or "gay" identity. Moreover, there are also individuals who engage in extensive homosexual behavior yet are not predominantly aroused by homosexual stimuli or do not consider themselves to "be" homosexual, such as male adolescents who have sex with men for money. Thus, one must pay attention to the empirical evidence regarding disjunctions between sexual orientation and sexual identity.[29]

With regard to gender identity, gender role, and sexual orientation, there are large normative sex differences. For example, almost all biological males have a male gender identity and almost all biological females have a female gender identity. Along similar lines, the vast majority of biological males are attracted sexually to biological females and the vast majority of biological females are attracted sexually to biological males. Understanding the mechanisms that underlie these normative sex differences is crucial in thinking about the mechanisms for atypical groups, as in the various intersex syndromes. In other words, it is important to keep in mind what is known about normative, empirical behavioral sex differences.[4]

Which Sex? Which Gender?

A common aspect of several physical intersex conditions involves the differentiation of ambiguous external genitalia. When this occurs, there is often uncertainty whether the neonate's *sex assignment* should be designated as male or female and the *gender assignment* that of a boy or a girl. Not surprisingly, such uncertainty often causes anxiety in parents and in the professional involved in determining a newborn's sex, whether that professional is a physician or nurse working in the modern hospital delivery room or a midwife working in some remote "third world" community far removed from the postmodern Western scene. Many contemporary physicians have characterized this uncertainty as a "medical" and "psychosocial" emergency that requires immediate attention and resolution,[30] perhaps reminiscent of a remark made in 1911 by Tuffier and Lapointe, who wrote, in a French gynecology journal, that "For hermaphrodites as well as for normal subjects, the possession of a [single] sex is a necessity of our social order."[31]

That the sex of a newborn is important should surprise no one. This fact has even been documented by empirically-minded scientists. In one study, Intons-Peterson and Reddel[32] had "parent-collaborators" call their friends following the birth of their babies. Overall, 80% of the initial questions were about the baby's sex. The single most frequently asked question was "Is it a boy or a girl?"

Sex and gender assignment at birth are believed to be the first of a cascade of events that fall under the rubric of *gender socialization*;[3] nowadays, with the development of techniques such as amniocentesis and ultrasound, parents can acquire information about fetal sex, which likely generates a variety of specific feelings and thoughts about their future child. Following these first events, whether they occur prenatally or after parturition, parents often select a name for their newborn that has a stereotypical masculine or feminine connotation. Many books are available to aid parents in these selections, the popular press routinely reports on the most common given names of boys and girls, and there are scholars who actually study the psychology and sociology of naming.[33] It is also common for parents to dress male and female infants in sex-stereotypical ways, including the North American tradition of sex-dimorphic "color coding" in pink or blue that began in the 1920s.[34] In one study, conducted in the early 1980s, researchers observed in-

fants at a shopping mall in Long Island, New York, and found that about 75% of the females had at least some pink in their clothing, compared to 0% of the males, and that 79% of the males had at least some blue in their clothing compared to only 8% of females.[35]

Sex assignment and subsequent "rearing" as a boy or girl have long been viewed as powerful socialization influences that account for sex differences in psychosexual differentiation. Thorne,[36] for example, argued that:

> While many still see gender as the expression of natural differences, the women's movement of the 1970s and 1980s launched a powerful alternative perspective: notions of femininity and masculinity, the gender divisions one sees on school playgrounds . . . the idea of gender itself—*all* are social constructions. . . . Parents dress infant girls in pink and boys in blue, give them gender-differentiated names and toys, and expect them to act differently. . . . peer groups . . . also perpetuate gender-typed play and interaction. In short, if boys and girls are different, they are not born, but *made* that way. (p. 2)

In stark contrast to this view, theorists with a biological bent also emphasize single-factor influences. For example, Swaab, Gooren, and Hofman[37] asserted that gender identity is very difficult to change, "probably because . . . [it is] fixed in the brain" (p. 52).

But because the rearing of an infant as a boy or a girl is usually perfectly confounded with biological sex, researchers have long made the point that it is actually difficult to disentangle the relative contribution of biological and psychosocial influences. For some researchers, it was this methodological and interpretive dilemma that led to the study of children with physical intersex conditions in the hope of providing at least a partial resolution to this problem.

Initial Empirical Studies: The Work of Money and Colleagues

Beginning in the 1950s, Money and colleagues began to report data on the psychosexual development of children born with physical intersex conditions.[38] It was noted that since hermaphrodites are "neither exclusively male or female, [they] are likely to grow up with contradictions existing between the sex of assignment and rearing, on the one hand, and various physical sexual variables, singly or in combination, on the other" (p. 333). Thus, Money and his colleagues asked "whether the gender [identity] that a hermaphrodite establishes during the course of growing up is concordant with the sex of assignment and rearing, or whether it is predominantly concordant with one or another of the . . . physical sexual variables" (p. 333).

In one study, conducted in the late 1950s,[38] it was found that only 5 of 105 patients with hermaphroditism had a "gender [identity that] was ambiguous and deviant from the sex of assignment and rearing" (p. 333). Thus, Money concluded that "the sex of assignment and rearing is consistently and conspicuously a more reliable prognosticator of a hermaphrodite's gender [identity] than is the chromosomal sex, the gonadal sex, the hormonal sex, the accessory internal reproductive morphology, or the ambiguous morphology of the external genitalia" (p. 333). Money et al[38] offered one additional finding for the relative importance of socialization factors in determining gender identity differentiation among children with physical intersex conditions:

> The clinching piece of evidence concerning the psychologic importance of the sex of assignment and rearing is provided when, among persons of identical physical diagnosis, some are reared as boys, some as girls. It is indeed startling to see, for example, two children with female [congenital adrenal hyperplasia] in the company of one another in a hospital playroom, one of them entirely feminine in behavior and conduct, the other entirely masculine, each according to upbringing. (p. 334)

Given such evidence for the apparent malleability and plasticity in gender identity differentiation, it became necessary to replace the reliance on identifying the patient's "true sex" with a different model for guiding decisions about gender assignment. As summarized by Meyer-Bahlburg,[20] the model developed by Money and the Johns Hopkins school of pediatric endocrinology can be characterized as the *optimal gender* policy of psychosocial and medical management. This policy aimed to result in the best possible prognosis with regard to six variables, which are shown in Table 2.

Appraisal of the Gender Identity Formation Data

To what extent have the original Money data been substantiated by subsequent research on gender identity formation in children with physical intersex conditions? To answer this question, one can take advantage of the increased precision in identifying physical intersex conditions on a syndrome-by-syndrome basis. Moreover, one can consider the nature of the syndromes themselves and which aspects of physical sex differentiation are affected in each.

It is with regard to those physical intersex conditions in which there might be some uncertainty at birth regarding sex assignment that the relative importance of gender socialization can best be evaluated. In genetic females, the syndrome of congenital adrenal hyperplasia (CAH) is most relevant; in genetic males, the relevant syndromes include steroid 5α-reductase 2

Table 2. Parameters of the Optimal Gender Policy of Psychosocial and Medical Management of Infants and Children with Physical Intersex Conditions

1. Reproductive potential (if attainable at all)
2. Good sexual function
3. Minimal medical procedures
4. An overall gender-appropriate appearance
5. A stable gender identity
6. Psychosocial well-being

Derived from Meyer-Bahlburg.[20]

deficiency (5-ARD), partial androgen insensitivity syndrome (pAIS), micropenis, penile agenesis (aphallia), and cloacal exstrophy. Regarding gender identity differentiation, these syndromes share two characteristic features: 1) there may be some uncertainty regarding sex assignment at birth, in part because the configuration of the external genitalia is severely affected and, as a result, there may be some uncertainty regarding the "optimal" gender in which the child should be reared; and 2) either the prenatal hormonal milieu or the configuration of the external genitalia (and sometimes both) can be atypical in relation to the gender in which the child is reared.

Congenital Adrenal Hyperplasia in Genetic Females

The syndrome of CAH has been one of the better studied intersex conditions from a psychosexual point of view. In genetic females with CAH, the overproduction of androgenic steroids during fetal development causes genital masculinization ranging from mild clitoral enlargement to complete fusion of the labioscrotal folds with a phallic urethra. It is this aspect of the syndrome that, at times, creates uncertainty with regard to sex assignment at birth. When the condition is properly diagnosed, several medical interventions typically ensue, including surgical "feminization" of the masculinized clitoris and cortisone-replacement therapy to control or eliminate postnatal virilization. Under these conditions, a female sex assignment is made and the infant is, invariably, raised as a girl.

Gender Identity Differentiation in Childhood

What do we know about the gender identity development of girls with CAH raised under these conditions? Based on several studies conducted over the past 30-plus years, we can conclude that the vast majority of girls with CAH appear to develop a female-typical gender identity.[39–42]

Gender Identity Differentiation in Adulthood

Adult follow-up of women with CAH provides a more definitive picture with regard to gender identity differentiation. Although gender identity conflict or confusion can certainly be ascertained in children and adolescents, one should note that the process of gender change is often long and complex. For example, in women without known somatic intersexuality who go through gender reassignment, i.e., female-to-male transsexuals, the mean age at transition is usually in the mid-20s.[43] Over the years, there have been several follow-up reports pertaining to the gender identity development of women with CAH.

In one study, our group assessed the gender identity of 31 women with CAH (mean age, 24.4 yrs) and 15 sister/female cousin controls (mean age, 25.6 yrs).[44] Gender identity was assessed via a semistructured interview and by a Gender Dysphoria/Identification self-report questionnaire. At the time of assessment, all of the probands were living, in the broadest sense, as women, i.e., they were known to others as females and were registered as such on legal or other official documents. For the interview ratings of current and lifetime gender dysphoria, the proband-control comparisons were not significant. On the self-report questionnaire, the two groups did not differ on the factor labeled Gender Dysphoria.

Although these data did not provide any clear evidence for gender dysphoria or discontent among the CAH probands, it should be noted that there were 10 additional potential probands who refused to participate in the study and 13 others could not be traced (including one who had died, and two who were raised as boys from infancy by parental decision). One of the refusers, age 19 yrs, had been previously assessed by me (in another hospital setting) because of extreme gender dysphoria. This patient was diagnosed with transsexualism (with a homosexual sexual orientation) using the criteria in the DSM-III-R.[45] Thus, of the 53 potential probands (excluding the one who had died in infancy), 3 (5.7%) were currently living as men.

This percentage was compared to one prevalence estimate of female-to-male transsexualism in genetic females, 1 in 30,400 (0.0000329%).[46] Using this baseline prevalence value, the odds ratio was 1823.70:1 that a genetic female with CAH in our sample was living, as an adult, in the male social role compared to genetic females in the general population living in the male social role (if we exclude the two CAH patients reared as boys from infancy, the odds ratio was 607.9:1).

Our group data appear to be comparable with other reports on the gender identity status of adult females with CAH.[47–48] These studies indicate (or imply) that the vast majority differentiated a female gender identity. One early study of women with CAH is of particular interest. In the late 1960s, Ehrhardt, Evers, and Money[49] reported the results of a study of 23 women with CAH (mean age, 33 yrs) who were "late-treated,"

i.e., they did not receive early corticosteroid replacement therapy and thus had lived for many years with the "stigma of heavy virilization, sometimes uncorrected genital morphology and lack of feminine secondary sexual development" (p. 117). The mean age of treatment onset with cortisone was 26 years (range, 8–47 yrs). All were living as women and none were judged to be severely gender dysphoric.

In most cohorts of patients, a percentage of genetic females with CAH were assigned to the male sex at birth (invariably due to the extreme masculinization of the external genitalia) and subsequently raised as boys without apparent complications. For example, in one large cohort, Mulaikal, Migeon, and Rock[50] reported that 9 (5.6%) of 158 genetic females with CAH were assigned to the male sex and reared as boys. Genetic females with CAH reared as boys is interesting in its own right because it tells us that a male gender identity can differentiate in a person who, for example, has female sex chromosomes and internal reproductive structures. It is likely that the masculinization of the external genitalia, which goes "uncorrected," works in concert with masculine gender socialization.

More interesting, however, are the cases of gender change from female to male that occur gradually over the life course at the instigation of the person with CAH, not others. Recently, Meyer-Bahlburg et al[51] reviewed this aspect of the CAH literature and presented data on four new patients in which this type of transformation occurred. Meyer-Bahlburg et al identified four factors that appeared contributory: 1) lack of surgical feminization or delay beyond infancy; 2) poor adherence to glucocorticoid replacement therapy, resulting in progressive physical virilization; 3) markedly masculine childhood gender role behavior; and 4) sexual attraction to females.

Other Aspects of Psychosexual Differentiation

Although the data on gender identity differentiation in genetic females with CAH suggests the importance of the psychosexual rearing environment in producing a female gender identity in the majority of cases, the picture is more complicated when one looks at other aspects of psychosexual development. There is now considerable evidence that the gender role behavior of CAH girls is masculinized; that is, these girls show, on average, a shift in the direction of male-typical interests and activity preferences.[52] Many researchers interpret this shift as a result of the masculinizing effect of the excess prenatal exposure to adrenal androgens, consistent with a very large body of experimental research on the role of prenatal sex hormones in affecting the sex-dimorphic behavior of lower animals.[53]

One example of this shift is with regard to sex-typed play behavior. Compared to unaffected sisters and female cousins, girls with CAH play more with male-typical toys and less with female-typical toys (Fig. 1).[54] Berenbaum[52] has documented similar shifts with regard to several other behavioral domains, including masculinized activity interests among adolescents with CAH, masculinized playmate preference, increased rates of aggression, better spatial ability, and decreased "maternalism" or interest in babies. In addition, women with CAH are more likely to report either a bisexual or a homosexual sexual partner preference, either in behavior or in fantasy, than are unaffected same-sex controls.[44,47]

The data on sexual orientation are particularly important to mention, in part because there is a tendency in the literature to overstate what is known about this particular aspect of CAH. For example, one might find in the literature an exaggeration of the rate of a bisexual or homosexual sexual orientation. If one takes the empirical literature at face value, it should be emphasized that the majority of CAH women appear to be heterosexual. On the other hand, one could argue that the rates of bisexuality or homosexuality are underestimates. For example, most follow-up studies of women with CAH have assessed patients in their early 20s and there is always the problem of underreporting for reasons pertaining to social desirability, that is, discomfort in reporting an atypical sexual orientation. Thus, there is a great deal more to be learned about the sexual orientation of women with CAH.

In summary, the data on genetic females with CAH generally support Money's original claim that gender identity differentiates primarily in accordance with gender of rearing. Nonetheless, there appears to be variability in the extent to which females with CAH are satisfied or content with their gender identity, and such variability appears to be greater than what is observed among control females.

Gender Identity Differentiation in Other Intersex Syndromes

Given the overall picture on gender identity differentiation among women with CAH, it is reasonable to ask why clinical management decisions regarding sex and gender assignment for newborns with physical intersex conditions appear to have fallen into a state of such general uncertainty.

The answer is threefold: first, there have always been case reports in the literature in which the initial sex assignment did not hold and the patient initiated a change from living in one gender to another;[55] second, data on other physical intersex conditions suggest a more variable empirical picture with regard to

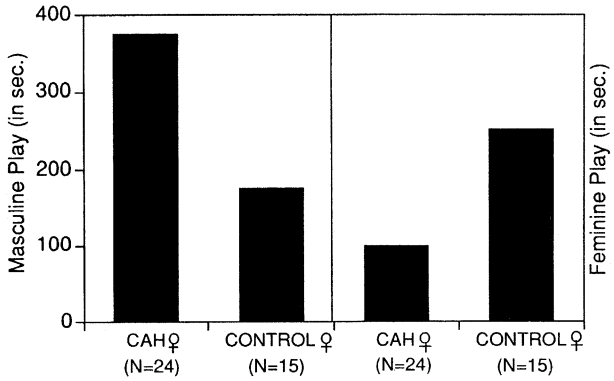

Fig. 1. Time spent playing with sex-typed toys by girls with congenital adrenal hyperplasia (CAH) and control girls during 10 minutes of play (play with neutral toys not shown). Data from Berenbaum and Hines.[54]

gender identity differentiation (see below); and third, the now famous David Reimer case has been used, at least in some quarters, to challenge the entire theoretical edifice underlying sex- and gender-assignment decisions for infants born with physical intersex conditions.[6,9,16] Regarding the Reimer case, for which the reader can find detailed consideration elsewhere,[56–58] it should be noted that a similar case had a very different outcome with regard to long-term gender identity differentiation.[59]

Consider the case report literature in which the initial gender assignment did not hold. There are three ways to make sense of this literature. First, it is conceivable that the importance of sex of rearing carries less weight than originally thought and certain biological factors override an environmental influence. Second, it is also conceivable that psychosocial factors, such as prolonged uncertainty about the patient's gender assignment, are contributory, that is to say, there was an inconsistent, if not ambivalent, early psychosexual rearing environment.[24,60] Third, and in my view, the most important factor to consider in such cases is whether or not they represent the exception or the rule.[61] This is particularly important for those intersex syndromes for which we have little in the way of systematic outcome studies. Regarding this last point, the problem here is the mirror image of what has been termed the "file drawer" problem in experimental research.[62] For a long time, it has been known that journals are inclined to publish the results of "successful" experiments. Unsuccessful experiments are relegated to the file drawer. Because published findings may overestimate the success of a particular line of research, quantitative procedures were developed for computing the tolerance for filed and future null results.[62] But given the current crisis in the field of intersexuality, the file drawer problem is the exact opposite, namely, that cases of "unsuccessful" rearing are more likely to be published than successful cases, at least nowadays, because it is the unsuccessful cases that are deemed newsworthy. One example of this pertains to mixed gonadal dysgenesis (MGD). Over the last five years, there have been at least three case reports in the literature that describe a gender change from female to male.[63–65] Yet, to my knowledge, there are no systematic group studies of gender identity differentiation in patients with MGD, so we really do not know if these cases are the rule or the exceptions.

It is with regard to several other intersex conditions (e.g., steroid 5α-reductase 2 deficiency [5-ARD], partial androgen insensitivity syndrome [pAIS], the micropenis syndromes, penile agenesis, and cloacal exstrophy) that affect genetic males for which there is greater uncertainty about gender identity differentiation. These syndromes share certain commonalities: in all instances, the appearance of the external genitalia is affected—either the phallic structure is small or ambiguous in appearance or, as in the case of penile agenesis, completely absent. Although androgen resistance occurs in some of these syndromes, it is believed that prenatal androgen exposure is greater than that which occurs in somatically normal genetic females and, in some instances, is likely comparable to somatically normal genetic males.[56]

The clinical decision, then, regarding gender assignment involves the following: Does one recommend raising the infant with a very tiny penis or no penis at all as a boy, with all of the putative hardships that might entail, or does one recommend raising the infant as a girl, which would call for castration, surgical creation of a neo-vagina, and feminizing hormone therapy? If one recommends the latter, what effect, if any, does the prenatal androgen exposure have on psychosexual differentiation? If one peruses the available empirical literature, it will be apparent that both approaches have been tried. The main problem in drawing definitive conclusions is that these syndromes, perhaps with one exception, have been studied much more poorly than has been the case with CAH. The exception is with regard to 5-ARD.

In 5-ARD, an impairment of steroid 5α-reductase activity during fetal development leads to an underproduction in plasma dihydrotestosterone, which causes the incomplete masculinization of the external genitalia. Because testosterone production is unaffected, masculinization of the internal reproductive structures is normal. Moreover, at puberty, there is relatively normal physical masculinization—both primary and secondary sex characteristics develop along male lines.

In behavioral sexology, 5-ARD began to receive a great deal of attention in the early 1970s. At that time, Imperato-McGinley and colleagues[66] described a cohort of affected individuals from the Dominican Republic in which the prevalence of the condition was

unusually high because of inbreeding, who showed a gradual change in gender identity from female to male, i.e., they "switched" from living as girls/women to living as boys/men. It was noted that newborns with 5-ARD were often assigned to the female sex and subsequently "raised as girls." At puberty, the girls' physical masculinization was so striking that they became known locally as "guevedoces"—penis at 12 (years of age). Of 18 subjects "unambiguously raised as girls . . . 17 of 18 changed to a male . . . gender identity . . . [during or after puberty]" (p. 1233). The data were summarized as follows:

> The 17 subjects who changed to a male . . . gender identity began to realize that they were different from other girls in the village between seven and 12 years of age, when they did not develop breasts, when their bodies began to change in a masculine direction and when masses were noted in the inguinal canal or scrotum. These subjects showed self-concern over their true gender. A male . . . gender identity gradually evolved over several years as the subjects passed through stages of no longer feeling like girls, to feeling like men and, finally, to the conscious awareness that they were indeed men. (p. 1234)

It was concluded that "the male sex drive appears to be testosterone related and not dihydrotestosterone related . . . and the sex of rearing as females . . . appears to have a lesser role in the presence of two masculinizing events—testosterone exposure in utero and again at puberty with the development of a male phenotype" (p. 1215). Since these initial reports, similar accounts of gender change from female to male in patients with 5-ARD have been described in samples from Papua New Guinea, Mexico, Brazil, and the Middle East (for review, see Zucker[56]).

In some quarters, the reaction to the initial report by Imperato-McGinley and colleagues was not to dispute the veracity of the gender change, but the explanation for it. These commentaries contained a great deal of discourse about the nature of the gender assignment at birth, particularly among post-first-generation probands. For these probands, the family and community had acquired some knowledge about the natural history of the condition, including the physical masculinization that occurred at puberty. Thus, for these probands, it was argued that they were not assigned unambiguously to the female sex and reared as girls, but that the culture created both "third sex" and "third gender" categories that would guide postnatal socialization.[67–68]

How are we to best interpret the phenomenon of gender change among individuals with 5-ARD? On the one hand, some have read the data as suggestive of a strong and direct effect of biological influences on gender identity differentiation. On the other hand, it has been argued that the evidence is more supportive of interaction effects: that is, genetic males with 5-ARD have, despite their ambiguous genitalia at birth, male-typical prenatal masculinization that predisposes to postnatal behavioral masculinity.[56] The response in the social environment augments this biological predisposition, which is augmented even further by the spontaneous physical masculinization that occurs at puberty. Among 5-ARD individuals raised from infancy as boys, the social environment certainly appears to work in concert with the putative prenatal masculinizing effects.[69]

How best to resolve these competing explanations? Here, it would be extremely useful to have natural history data on individuals with 5-ARD who are treated differently, both medically and psychosocially, than in the cultural groups noted above. For example, in the United States and Europe, it is possible that at least some 5-ARD individuals would be raised as girls on the grounds that the external genitalia will not masculinize sufficiently to permit comfortable (heterosexual) sexual functioning. Thus, in accordance with the optimal gender policy, such individuals would be castrated in infancy, receive surgical feminization of the genitalia, and be placed on feminizing hormones at puberty. In this respect, then, the situation would be comparable to the usual course of surgical, hormonal, and psychosocial events for girls with CAH. Unfortunately, we do not have a great deal of data about 5-ARD individuals treated in this manner. Wilson, Griffin, and Russell[70] (see also Wilson[71]) summarized some of the available data and it appears that there were fewer instances of gender change than that reported by Imperato-McGinley, whose patients, one must remember, were not treated medically (Table 3).

In recent years, we are learning more about gender identity differentiation for the other conditions, such as the micropenis syndromes, penile agenesis, and cloacal exstrophy. In thinking about these new data, it is important to bear in mind several facts. First, the number of systematic studies are still few in number. Second, some of these conditions are extremely rare; for example, with regard to penile agenesis, one estimate suggested a prevalence rate of only 1 in 10–30 million live births.[56] Third, for cloacal exstrophy, the condition was virtually always fatal up until around 1960; now, however, with astonishing advances in pediatric surgery, the survival rate in Western countries is very high, and we are just beginning to learn about long-term outcome.

In patients born with a micropenis, the available evidence suggests that gender identity differentiates as a function of sex of rearing, with no clear indication that patients reared as male are any more or less satisfied with their gender identity than patients reared as female.[56,72] In itself, this is an important finding and

points to the need to consider parameters other than gender identity outcome in making clinical management decisions.

At present, the data on gender identity differentiation in genetic males with cloacal exstrophy raised as girls appear quite confusing. Reiner,[73] for example, at Johns Hopkins Hospital in Baltimore reports a high rate of gender change in his patients; unfortunately, these data have not yet been published. In contrast, Schober and Ransley, at Great Ormond St. Hospital in London, England, have reported on a sample of 15 patients raised as girls (age 13–18 yrs) and find no instance of gender change, although these data too are also not yet published (J.M. Schober, personal communication, May 15, 2001). I have also had the opportunity to evaluate, over the past few years, two youngsters with cloacal exstrophy, age 12 yr, both raised as girls, with no clear evidence for marked gender dysphoria.

How might we interpret these conflicting data sets? First, one might note some commonalities. Most genetic males with cloacal exstrophy raised as girls appear to be tomboyish in their gender role behavior, just like one observes in girls with CAH.[74] The key question is how to resolve the discrepant results for gender identity. One possibility pertains to the postnatal rearing environment and subsequent clinical management. It is conceivable that, for some families, the idea of raising their youngster as a girl is accepted as a plausible possibility, whereas in other families the idea is more complex and uncertain. Thus, the postnatal rearing environment may interact with the biologic predisposition for behavioral masculinity.

Let me elaborate on this point: in both cloacal exstrophy cases that I assessed, detailed clinical interviews with the parents indicated that they accepted the physician recommendation at the time of birth for a female gender assignment with relative ease. For example, the father of one of the youngsters commented, "The doctor said that there was nothing 'down there' and that there was nothing he could do. He said it would be easier to raise the baby as a girl." In contrast, I recently assessed a 15-year-old youngster, born with penile agenesis, and gender assigned as a girl in infancy. Other medical complications precluded the youngster from living at home for the first two years. At that point, the youngster was raised by relatives (the mother was judged not capable of raising the baby and the biological father was absent). In this case, there was strong evidence for gender dysphoria, along with tomboyish behavior, and the youngster wanted to live as a boy. In the family matrix, it was clear that the adults who raised her never accepted the idea that she could be raised as a girl and this ambivalence permeated the clinical interview.

Table 3. Gender Identity Differentiation in Patients with 5-α-Reductase 2 Deficiency

	Raised Female	
Study	Female Gender Identity	Male Gender Identity
Imperato-McGinley et al[66]	1 (5.5%)	17 (94.5%)
Wilson et al[70]	19 (65.5%)	10 (34.5%)
	Raised Male	
Wilson et al[70]	0 (0.0%)	7 (100%)

A more detailed consideration of the empirical literature on gender identity differentiation in 5-ARD can be found elsewhere.[56]

Toward a Resolution: The North American Task Force on Intersexuality

Over the past 10 years, there have been important strides in both basic and applied research on intersexuality, as well as a great deal of discussion about clinical care. There are more investigators interested in the topic. Although the field is in a great deal of flux, and despite the attendant anxiety that this disequilibrium elicits, it is also an exciting time. Research on sex and gender matters has become more respectable. The field owes a great deal to its critics, who have prodded researchers and clinicians to invest more time in addressing the urgent questions that need to be answered.

In 1999, Ian Aaronson, a pediatric urologist at the Medical School of South Carolina, founded the *North American Task Force on Intersexuality* (natfi@musc.edu). This multidisciplinary task force has as its mission the development of multicenter empirical studies designed to answer some of the most pressing questions about long-term outcome for patients born with physical intersex conditions. It is clear that cross-center collaboration is vital in order to generate sample sizes with sufficient statistical power that will allow us to answer these questions, including gender identity differentiation, the effects of surgical interventions on sexual functioning, and general quality-of-life parameters.

As the field evolves, it is crucial for both researchers and clinicians alike to recognize the complexity of the factors involved in psychosexual differentiation. The seductive lure of either psychosocial or biological reductionism remains a very strong temptation, to which many players in the field succumb. Recent advances in the field of animal sexology point to the importance of paying serious attention to multifactorial models in our understanding of psychosexual differentiation in humans. For example, Juraska[75] has shown how the typical sex difference in the number of neurons in the corpus callosum of rats is ex-

quisitely sensitive to, and modified by, the rearing environment. Breedlove[76] has shown that copulatory experience in rats altered neural morphology, suggesting the possibility that differences in sexual behavior cause, rather than are caused by, differences in brain structure. In nonhuman primates, Wallen[77] has summarized ways in which the social environment either attenuates or exacerbates typical sex differences in behavior, thus providing illustrations of how "nature needs nurture." Thus, it is in the more precise identification of the transactional nature of biological and psychosocial influences on gender identity differentiation in particular, and psychosexual differentiation in general, that future empirical inquiry must continue to invest its efforts.

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